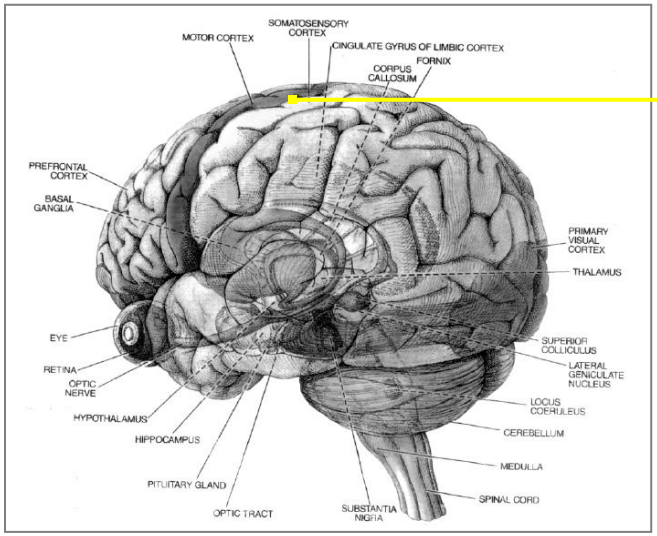
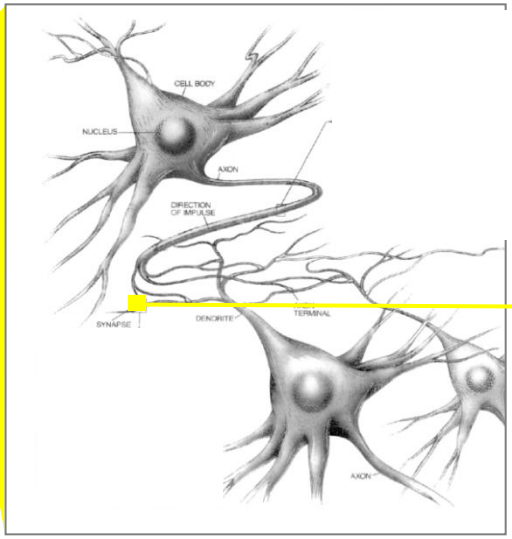
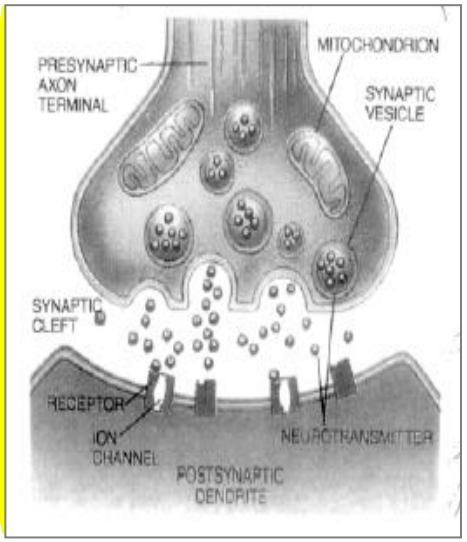
Brain

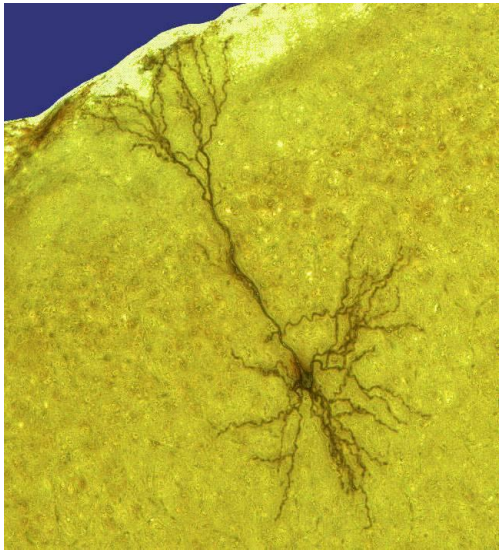


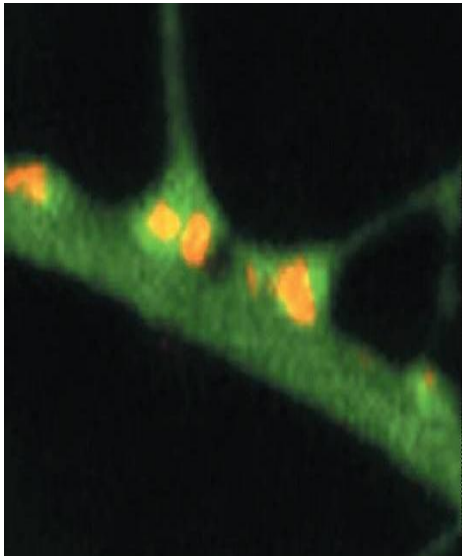
Neuron



Synapse



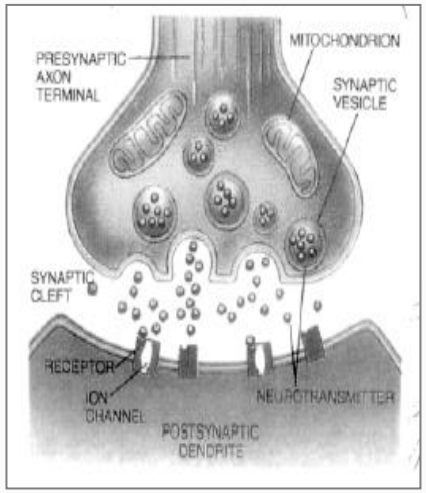


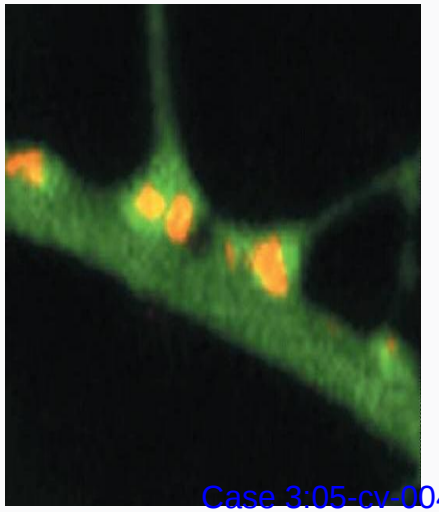


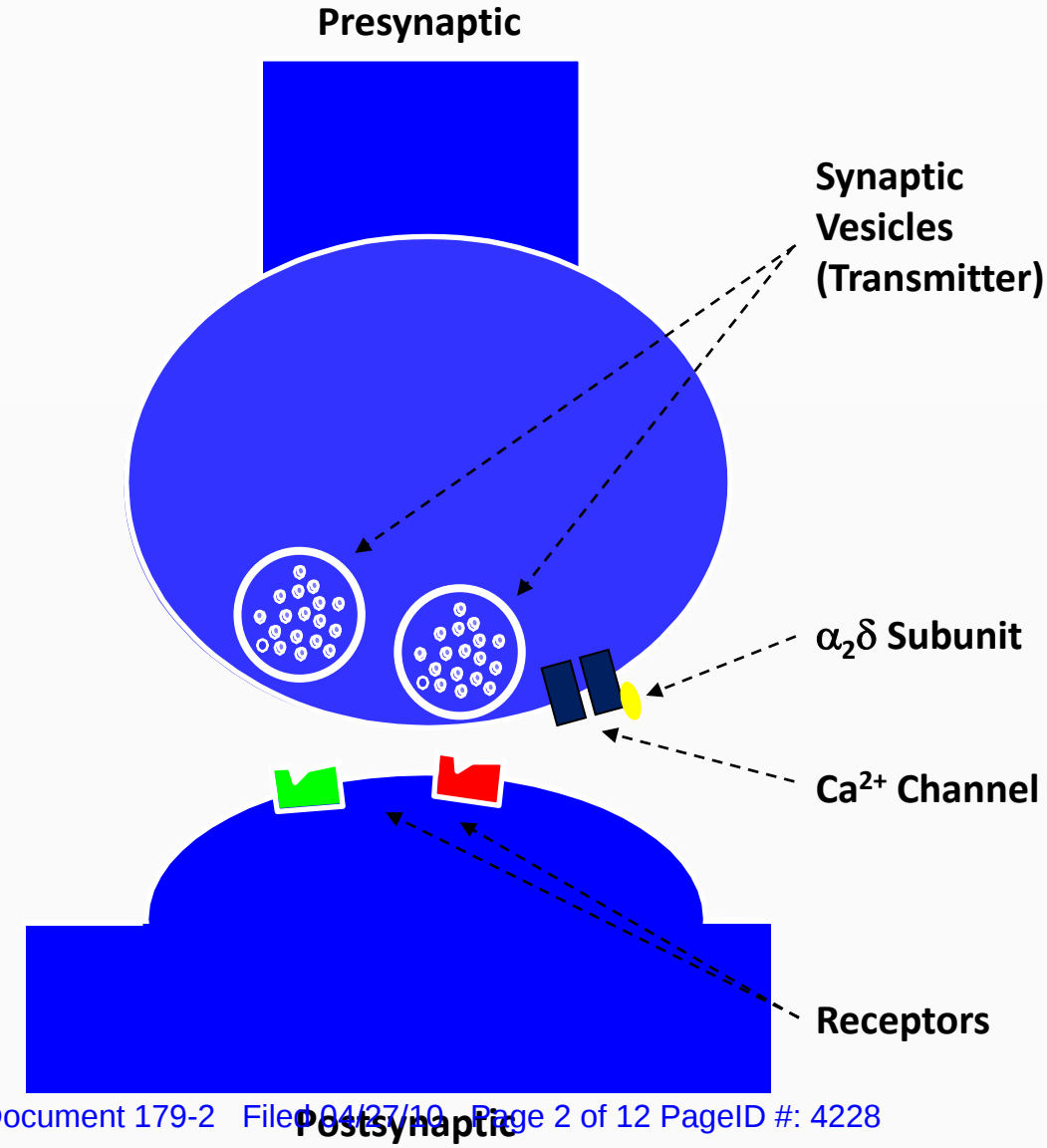
Source: U.S. Dep't. of Health & Human Services., Mental Health: A Report of the Surgeon General 34-35 (1999); T.A. Ryan (2001) Curr. Opin. Neurobiology 11:544-49

Synapse: Basic Parts and Function

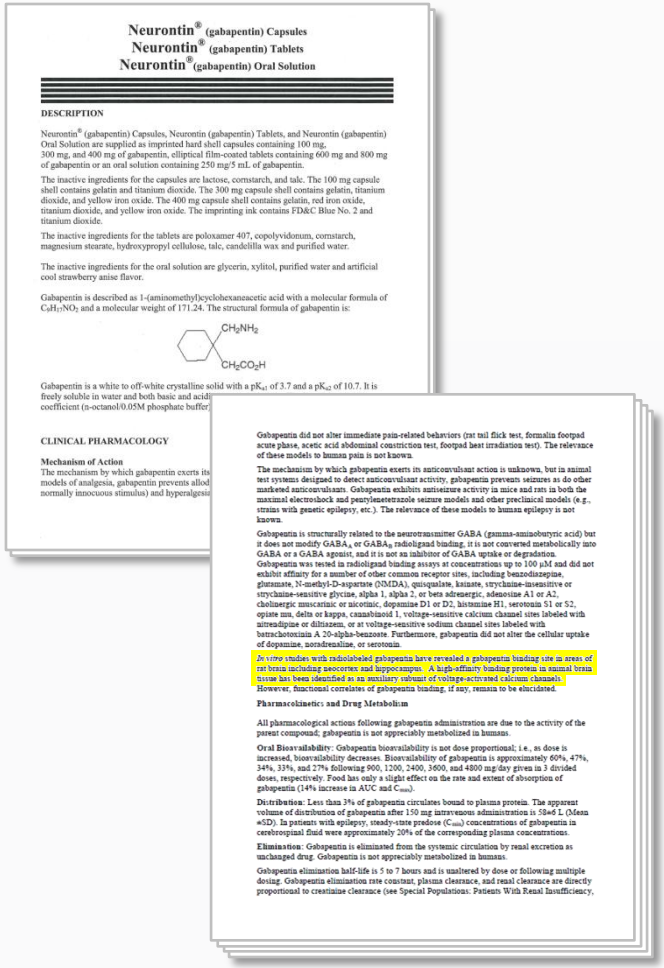
Synapse







FDA Labeling: Calcium Channel Subunit (α_2-δ) Is the Molecular Target for Neurontin



Neurontin® (gabapentin) Capsules
Neurontin® (gabapentin) Tablets
Neurontin® (gabapentin) Oral Solution

DESCRIPTION

Neurontin® (gabapentin) Capsules, Neurontin (gabapentin) Tablets, and Neurontin (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

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Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The structural formula of gabapentin is:

Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidi
coefficient (n-octanol/0.05M phosphate buffer

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism by which gabapentin exerts its
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Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 μM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

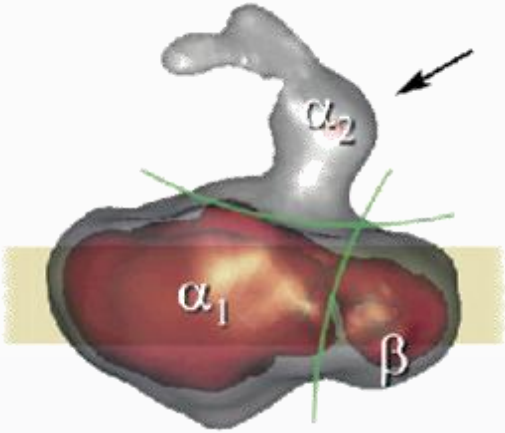
Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

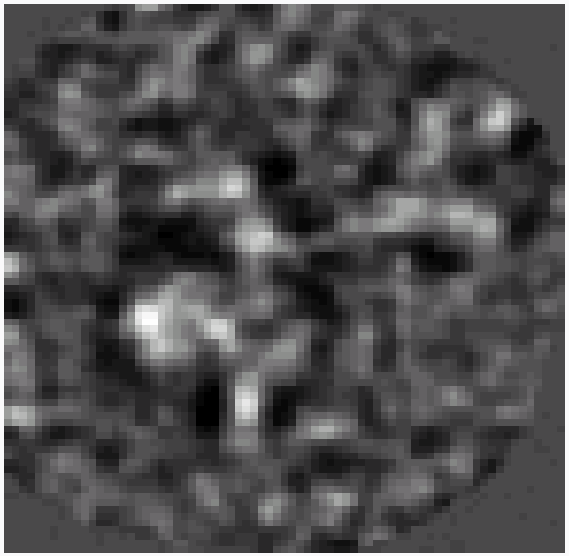
Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations: Patients With Renal Insufficiency,

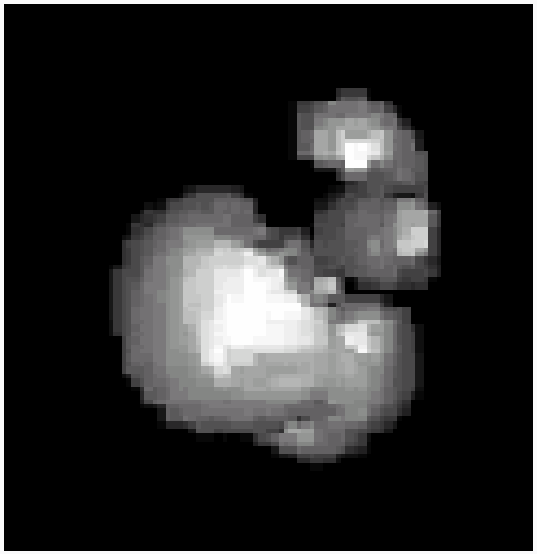
"In vitro studies with radiolabeled gabapentin have revealed a **gabapentin binding site** ... in animal brain tissue ... an auxiliary **subunit of voltage-activated calcium channels**."

Source: Neurontin U.S. Package Insert at 2 (Jan. 2007)

Calcium Channels: (α_2-δ) Site

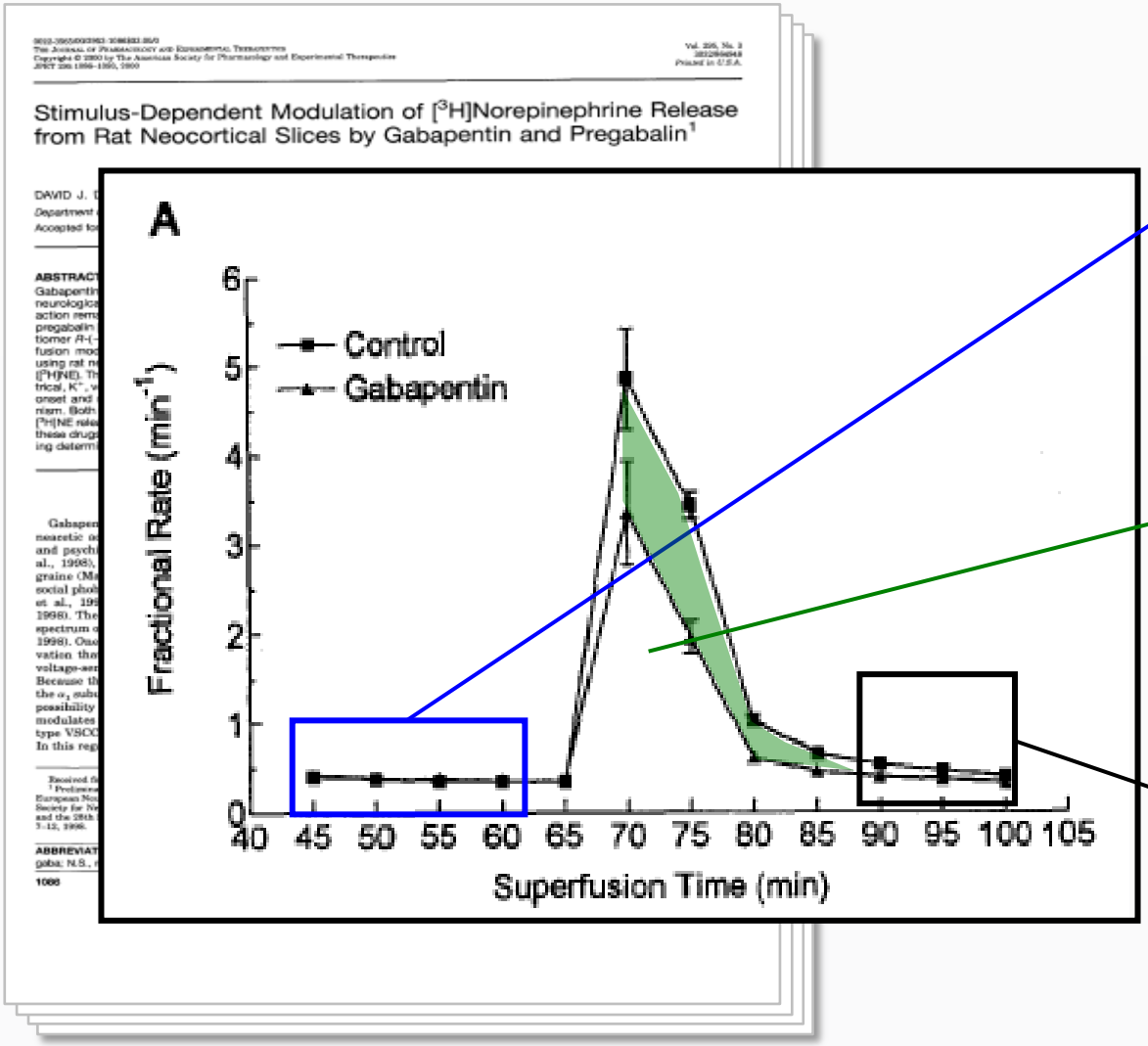






Source: Wolf, et al., J Mol. Biol. 332:171 (2003)

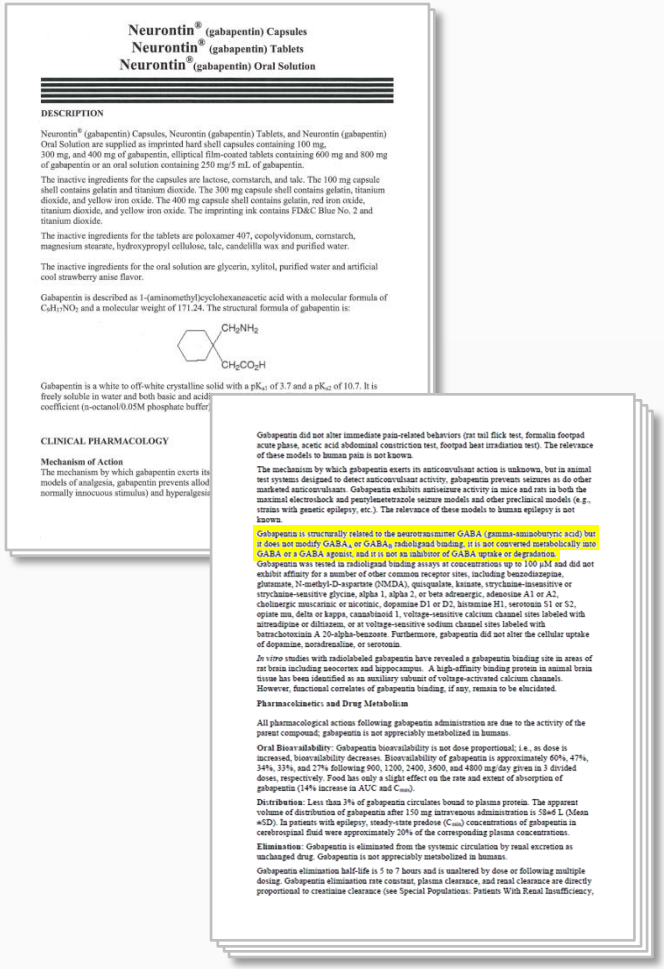
Neurontin Affects Only Artificially Stimulated Excess Monoamine Release



- **Without stimulus, Neurontin had no effect**
- **During stimulus, Neurontin modulated excess release**
- **After stimulus, Neurontin had no effect**

Source: Dooley, et. al. (2000)

FDA Labeling: No GABAergic Activity and No GABA Molecular Target for Neurontin



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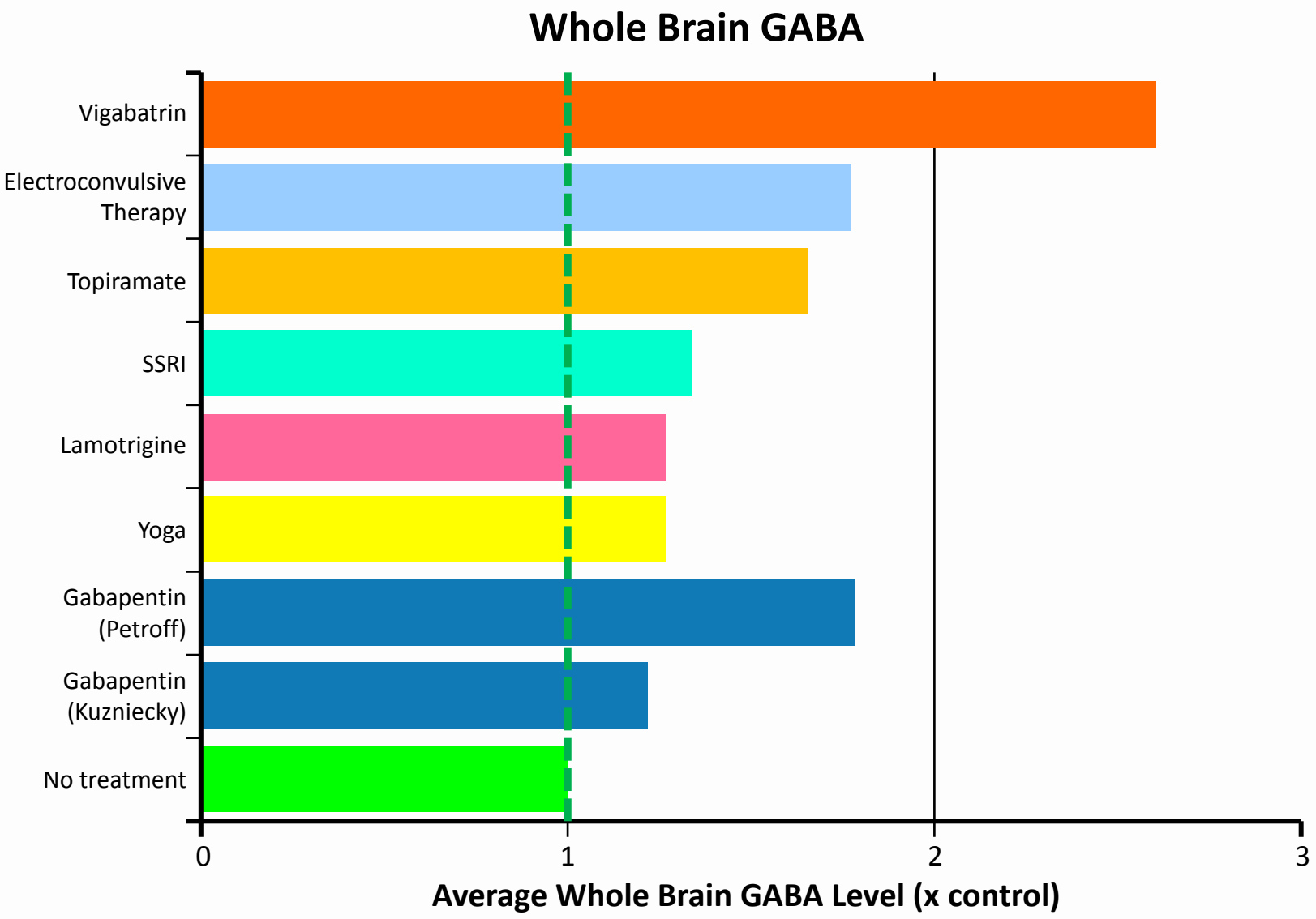
Source: Neurontin U.S. Package Insert at 2 (January 2007)



Source: Kuzniecky, et al. (2002); Petroff, et al. (2007); Streeter, et al. (2007); Sanacora, et al. (2002); Sanacora, et al. (2003); Petroff, et al. (1998)

Neurontin Is Not a GABA Agonist

Gabapentin is not a $GABA_B$ receptor agonist

The Anticonvulsant Gabapentin (Neurontin) Does Not Act through γ-Aminobutyric Acid-B Receptors

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MOLECULAR PHARMACOLOGY
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Mol Pharmacol 61:1377–1384, 2002

ANDERS A. JENSEN, JOHANNES MOSBACHER, SUSANNE ELG, KURT LINGENHOEHL, TANIA LOHMANN, TOMMY N. JOHANSEN, BJARKE ABRAHAMSEN, JAN P. MATTSSON, ANDERS LEHMANN, BERNHARD BETTLER,[1] and HANS BRÄUNER-OSBORNE

NeuroScience PharmaBiotec Research Centre, Department of Medicinal Chemistry, the Royal Danish School of Pharmacy, Copenhagen, Denmark (A.A.J., T.N.J., B.A., H.B.-O.); Novartis Pharma AG, Therapeutic Area Nervous System, Basel, Switzerland (J.M., K.L., T.L., B.B.); AstraZeneca R&D Mölndal, Cell Biology & Biochemistry (S.E., J.P.M.) and Gastrointestinal Biology, Integrative Pharmacology (A.L.), Mölndal, Sweden; and Departamento de Fisiologia e Biofísica, Instituto de Ciências Biomédicas, USP, São Paulo, Brazil (T.L.)

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ABSTRACT

The actions of the anticonvulsant gabapentin [1-(aminomethyl)-cyclohexaneacetic acid, Neurontin] have been somewhat enigmatic until recently, when it was claimed to be a γ-aminobutyric acid-B ($GABA_B$) receptor agonist acting exclusively at a heterodimeric complex containing the $GABA_{B(1a)}$ splice variant (*Mol Pharmacol* 2001;**59**:144–152). In this study, we have investigated the effects of gabapentin on recombinant $GABA_{B(1a)}$ and $GABA_{B(1b)}$ receptors coexpressed with $GABA_{B(2)}$ in five different functional recombinant assays, its ability to inhibit [^{3}H]GABA binding in a $GABA_B$ receptor-selective binding assay using rat synaptic membranes, and its ability to inhibit transient lower esophageal sphincter relaxations in Labrador retriever dogs. Up to a concentration of 1 mM, gabapentin displayed no agonist activity in any of the assays. Gabapentin did not displace [^{3}H]GABA from $GABA_B$ receptor sites in rat synaptic membranes. Finally, in contrast to the classic $GABA_B$ receptor agonist baclofen, gabapentin was unable to inhibit transient lower esophageal sphincter relaxations in dogs. Because of high levels of $GABA_{B(1a)}$ in the canine nodose ganglion, this finding indirectly supports the inactivity of gabapentin on the $GABA_{B(1a,2)}$ heterodimer demonstrated in various in vitro assays. In light of these results, we find it highly questionable that gabapentin is a $GABA_B$ receptor agonist. Hence, the anticonvulsive effects of the compound have to arise from GABA$_B$ receptor-independent mechanisms.

The Anticonvulsant Gabapentin (Neurontin) Does Not Act through γ-Aminobutyric Acid-B Receptors

metabotropic $GABA_B$ receptors. The $GABA_B$ receptors belong to the family C of the G-protein-coupled receptor superfamily (Möhler and Fritschy, 1999; Marshall et al., 2000). Two receptors, $GABA_{B(1)}$ and $GABA_{B(2)}$, have recently been cloned, and several splice variants of both receptors have been identified (Kaupmann et al., 1997, 1998; Jones et al., 1998; White et al., 1998; Pfaff et al., 1999; Billinton et al., 2001).

$GABA_{B(1)}$ and $GABA_{B(2)}$ form heterodimers (Jones et al., 2001; Schuler et al., 2001). The majority of the $GABA_B$ heterodimer complexes are either of a $GABA_{B(1a,2)}$ or a $GABA_{B(1b,2)}$ composition, and the two $GABA_{B(1)}$ splice variants differ in their expression pattern and their pre- and postsynaptic localization (Kaupmann et al., 1997; Benke et al., 1999; Poorkhalkali et al., 2000; Prosser et al., 2001; Schuler et al., 2001).

Agonist binding to the $GABA_{B(1,2)}$ heterodimer has been demonstrated to take place in the amino-terminal domain of the $GABA_{B(1)}$ subunit (Galvez et al., 1999, 2000; Malitschek et al., 1999). The major part of this region shares a weak amino acid sequence similarity with a family of bacterial periplasmic binding proteins, as is the case for other family C

A.A.J. and H.B.-O. were supported by the Danish Medical Research Council. T.L. was supported by Fundação de Amparo á Pesquisa do Estado de São Paulo (FAPESP).

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ABBREVIATIONS: GABA, γ−aminobutyric acid; VFT, Venus flytrap; TLESR, transient lower esophageal sphincter relaxation; AEBSF, 3,4-(2-aminoethyl)benzenesulfonylfluoride; [Ca^{2+}]$_i$, intracellular calcium concentration; FLIPR, fluorescence imaging plate reader; HBSS, Hanks' buffered saline solution; CHO, Chinese hamster ovary; HEK, human embryonic kidney; IP, inositol phosphate; TC, Tris-calcium; HPLC, high-performance liquid chromatography; CGP54626, [S-(R*,R*)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; Kir, inwardly rectifying potassium channel.

Pergamon

Neuropharmacology 41 (2001) 965–975

NEURO PHARMACOLOGY

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Gabapentin is not a $GABA_B$ receptor agonist

Christophe Lanneau [a], Andrew Green [b], Warren D. Hirst [a], Alan Wise [b], Jon T. Brown [a], Emmanuelle Donnier [a], Kelly J. Charles [a], Martyn Wood [c], Ceri H. Davies [a], Menelas N. Pangalos [a,*]

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Received 11 June 2001; received in revised form 24 August 2001; accepted 29 August 2001

Abstract

Recent experiments have demoastrated that formation of functional type B gamma-aminobutyric acid ($GABA_B$) receptors requires co-expression of two receptor subunits, $GABA_{B1}$ and $GABA_{B2}$. Despite the identification of these subunits and a number of associated splice variants, there has been little convincing evidence of pharmacological diversity between $GABA_B$ receptors comprising different subunit combinations. However, Ng et al. [Mol. Pharmacol., 59 (2000) 144] have recently suggested a novel and important pharmacological difference between $GABA_B$ receptor heterodimers expressing the $GABA_{B1a}$ and $GABA_{B1b}$ receptor subunits. This study suggested that the antiepileptic GABA analogue gabapentin (Neurontin) is an agonist at $GABA_{B1a}$ receptors expressing the $GABA_{B1a}$ but not the $GABA_{B1b}$ receptor subunit. The importance of this finding with respect to identifying novel $GABA_B$ receptor ... to repeat these experiments in our own [^{35}S]−GTPγS binding and second messenger assay ... was completely inactive at recombinant $GABA_B$ heterodimers expressing either $GABA_{B1a}$ ... combination with $GABA_{B2}$ receptor subunits. In addition, in both CA1 and CA3 pyramidal ... we were unable to demonstrate any agonist-like effects of gabapentin at either pre- or ... contrast, gabapentin activated a $GABA_A$ receptor mediated chloride conductance. Our data ...$_B$-receptor agonist let alone a $GABA_B$ receptor subunit selective agonist. © 2001 Published ...

...$GABA_{B1a}$; $GABA_{B1b}$; Hippocampus

1. Introduction

Type B gamma-aminobutyric acid ($GABA_B$) receptors are present at pre- and post-synaptic loci throughout the central nervous system, where they inhibit adenylate cyclase activity, cause post-synaptic hyperpolarisation and inhibit neurotransmitter release (for review see Bowery, 1993; Couve et al., 2000; Billinton et al., 2001). The recent cloning of two $GABA_B$ receptor subunits, termed $GABA_{B1}$ and $GABA_{B2}$, which form functional receptors by heterodimerisation has raised the possibility that differences in $GABA_B$ receptor subunit composition may give rise to pharmacologically distinct receptor subtypes (Kaupmann et al., 1998a, 1998b, 1999; White et al., 1998; Jones et al., 1998; Kuner et al., 1999). A further source of pharmacological diversity may also arise from splice variants of these $GABA_B$ receptor subunits.

Two splice variants of the $GABA_{B1}$ subunit were originally described, termed $GABA_{B1a}$ and $GABA_{B1b}$, which differ in the extreme amino terminal domain (Kaupmann et al., 1997). Thus, the $GABA_{B1a}$ receptor subunit contains an extra sequence of 130 residues which encode two Sushi domains (Hawrot et al., 1998). Additional splice variants have now been described such as the human $GABA_{B1c}$ receptor subunit which lacks 62 resi-

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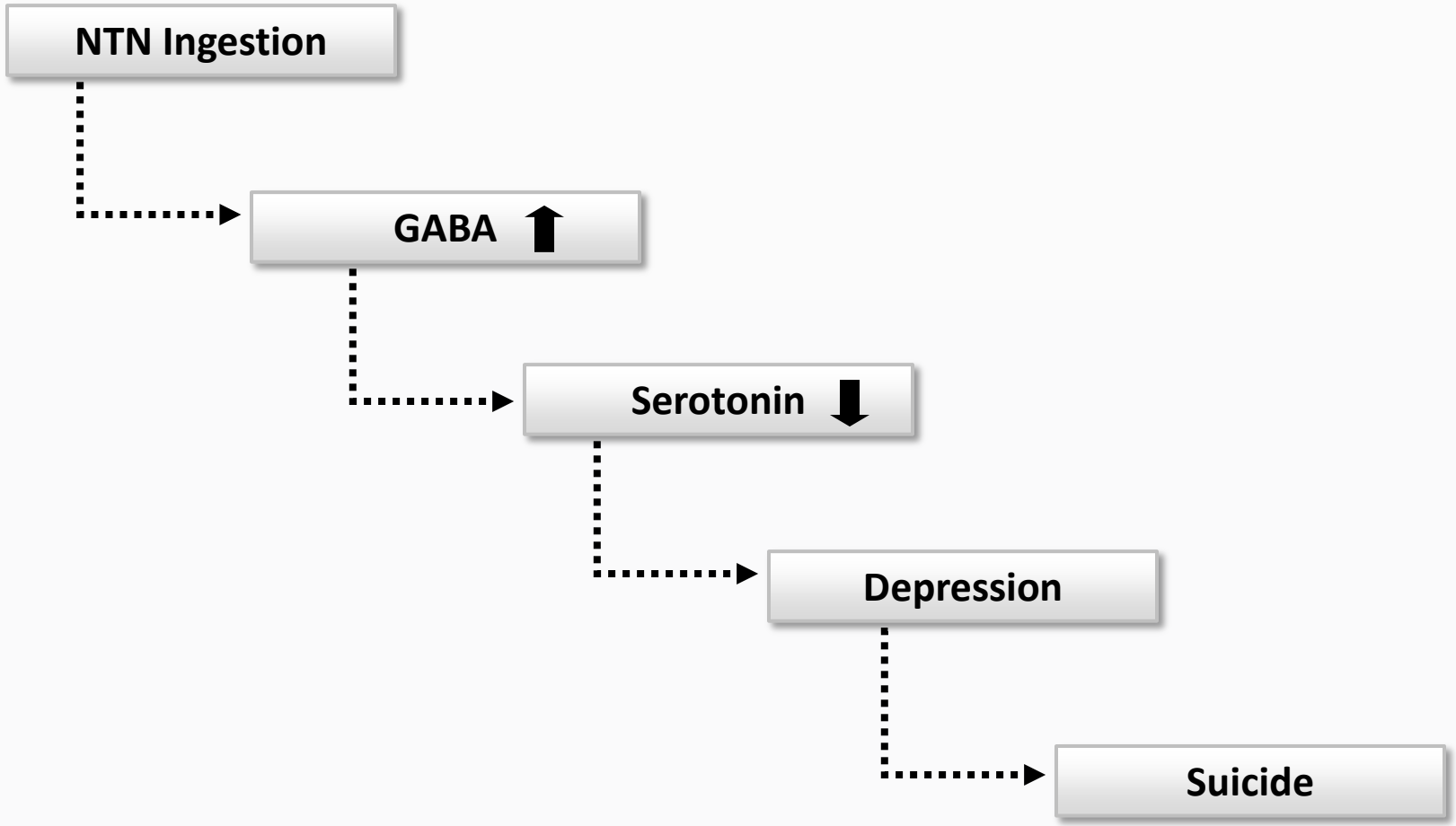
PII: S0028-3908(01)00140-X

Source: Jensen, et al., Mol Pharmacol. (2002); Lanneau, et al., Neuropharmacol. (2001)

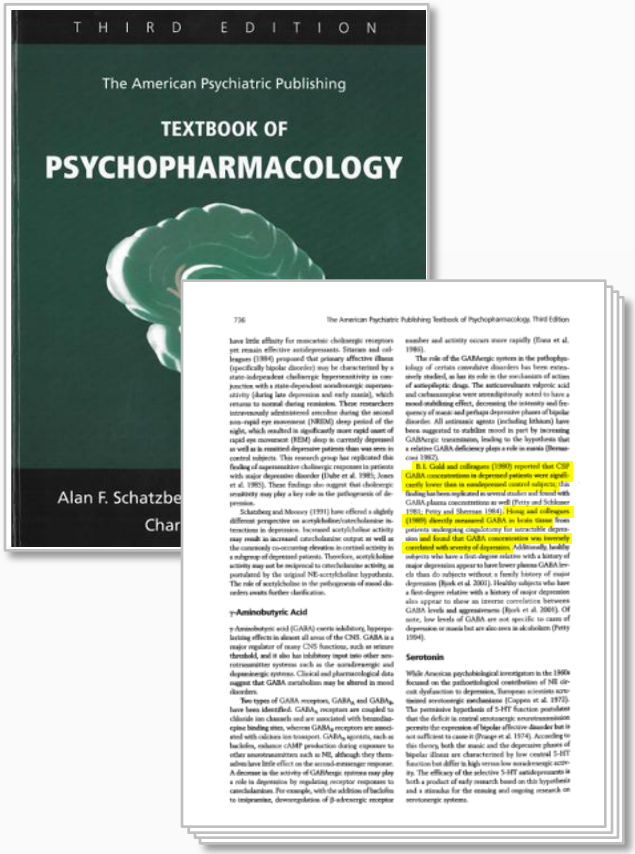
Plaintiff's Expert's Theory



Source: Deposition of Prof. M. Trimble 52:12-22 (Oct. 18, 2007)

Depression Is Associated With *Reduced* GABA, Not Increased GABA

2004



"B.I. Gold and colleagues (1980) reported that CSF **GABA concentrations in depressed patients were significantly lower** than in nondepressed control subjects. ...Honig and colleagues (1989) directly measured GABA in brain tissue ... and found that **GABA concentration was inversely correlated with severity of depression**."

Source: Schatzberg & Nemeroff, *Textbook of Psychopharmacology* 736 (3rd ed. 2004)

Neurontin Does *Not* Affect GABA or Serotonin Turnover (5-HIAA) in Human CSF

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EPILEPSY RESEARCH

Seizure frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures

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Abstract

Gabapentin (GBP) is a non-protein-bound gamma amino acid which is not subjected to metabolic degradation in man. As part of a placebo-controlled double-blind study, patients suffering from intractable complex partial seizures with or without secondary generalization were followed with lumbar punctures at baseline and after three months of GBP treatment (900 mg/day or 1200 mg/day). Cerebrospinal fluid (CSF) was analyzed for concentrations of GBP, amino acids including GABA, homovanillic acid (HVA), and 5 hydroxyindoleacetic acid (5-HIAA). The results indicate that there were no changes in the selected amino acids, HVA, or 5-HIAA after GBP treatment. At steady state the CSF/plasma ratios of GBP ranged from 0.056 to 0.34, indicating that there may be some type of active out-transport of GBP across the blood–brain barrier. No linear relationship was observed between plasma and CSF levels in these patients.

Keywords: Gabapentin; Complex partial seizure; Cerebrospinal fluid; Amino acid

1. Introduction

Gabapentin (GBP), 1-(aminomethyl)cyclohexaneacetic acid, is a new antiepileptic drug which has been shown to be an effective anticonvulsant in a variety of animal models and in large multicenter clinical trials [1,6,14], and is now approved for use in numerous countries including the USA. Although GBP chemically is a GABA analogue, it does not appear to be a GABA agonist or to have GABAergic properties. There is now evidence that GBP may bind to a specific novel receptor in the brain which is distinct from the GABA receptor subtypes [13]. After a single 900-mg or 1200-mg dose of GBP, only low concentrations of GBP found in the plasma were recovered in the cerebrospinal fluid (CSF) after 6 hours. After 24 hours, low concentrations of GBP

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"Cerebrospinal fluid (CSF) was analyzed for concentrations of GBP, amino acids including **GABA**, homovanillic acid (**HVA**), and 5-hydroxyindoleacetic acid (**5-HIAA**). The results indicate that there were **no changes** in the selected amino acids, HVA, or 5-HIAA **after GBP treatment**."

Source: Ben-Menachem, et al. (1995)

Summary of Opinions

- Neurontin acts directly at calcium-channel α_2-δ proteins
  - It does not increase GABA function
  - It does not act directly at sites unique to GABA or serotonin synapses
  - It does not change serotonin function
- Many diverse treatments increase whole brain GABA level and do not cause depression
  - SSRI medicines for depression
  - Some medicines for epilepsy
  - Electroconvulsive therapy for depression
  - Yoga exercise